## REMARKS

Claims 1-41 have been canceled without prejudice. Claims 42 thru 58 have been amended. Claims 59 thru 67 have been previously presented. Support for the amended claims can be found throughout the specification, claims and figures as originally filed. No new matter has been added by amendments to the claims.

Applicant now turns to comments made by the Examiner in the Office Action as follows:

1. The Examiner states, "Claims 42-67 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-7 and transgene constructs that directly reduce endogenous expression of chloride channels CIC-3 and CIC-6, wherein the cell exhibits higher levels of CIC-7 expression than that of CIC-3 or CIC-6,

b) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-7 and transgene constructs that directly reduce endogenous expression of chloride channels CIC-3, CIC-4, CIC-5, and CIC-6, wherein the cell exhibits higher levels of CIC-7 expression than that of CIC-3, CIC-4, CIC-5, and CIC-6,

c) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-7 and transgene constructs that directly reduce endogenous expression of chloride channels CIC-1, CIC-2, CIC-Ka, CIC-Kb, CIC-3, CIC-4, CIC-5, and CIC-6, wherein the cell exhibits higher levels of CIC-7 expression than that of CIC-1, CIC-2, CIC-Ka, CIC-Kb, CIC-3, CIC-4, CIC-5, and CIC-6,

d) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-3 and a transgene construct that directly reduces endogenous expression of chloride channel CIC-7, wherein the cell exhibits higher levels of CIC-3 and reduced levels of CIC-7,

e) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-4 and a transgene construct that directly reduces endogenous expression of chloride channel CIC-7, wherein the cell exhibits higher levels of CIC-4 and reduced levels of CIC-7,

f) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-4 and a transgene construct that directly reduces endogenous expression of chloride channels CIC-3, CIC-5, CIC-6, and CIC-7, wherein the cell exhibits higher levels of CIC-4 and reduced levels CIC-3, CIC-5, CIC-6, and CIC-7,

g) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-6 and a transgene construct that directly reduces endogenous expression of chloride channel CIC-7, wherein the cell exhibits higher levels of CIC-6 and reduced levels of CIC-7,

h) an in vitro cell comprising transgene constructs that overexpress the chloride channels CIC-3 and CIC-6 and a transgene construct that directly reduces endogenous expression of chloride channel CIC-7, wherein the cell exhibits higher levels of CIC-3 and CIC-6 and reduced levels of CIC-7,

i) an in vitro cell comprising transgene constructs that overexpress chloride channels CIC-1, CIC-2, CIC-Ka, CIC-Kb, CIC-3, CIC-4, CIC-5, and CIC-6 and a transgene construct that directly reduces endogenous expression of CIC-7, wherein the cell exhibits higher levels of CIC-1, CIC-2, CIC-Ka, CIC-Kb, CIC-3, CIC-4, CIC-5, and CIC-6 and reduced levels of CIC-7.

j) an in vitro cell comprising a transgene construct that overexpresses chloride channel CIC-6 and a transgene constructs that directly reduce endogenous expression of chloride channels CIC-3, CIC-4, CIC-5, CIC-7, wherein the cell exhibits higher levels of CIC-6 and reduced levels of CIC-3, CIC-4, CIC-5, and CIC-7,

k) method of screening for compounds, using the claimed in vitro cells, does not reasonably provide enablement for

a) any natural in vitro cells that exhibit:

1. higher levels of CIC-7 expression than that of CIC-3 or CIC-6,

2. higher levels of CIC-7 expression than that of CIC-3, CIC-4, CIC-5, and CIC-6,

3. higher levels of CIC-7 expression than that of CIC-1, CIC-2, CIC-Ka, CIC-Kb, CIC-3, CIC-4, CIC-5, and CIC-6,

4. higher levels of CIC-3 and reduced levels of CIC-7,

5. higher levels of CIC-4 and reduced levels of CIC-7

6. higher levels of CIC-4 and reduced levels CIC-3, CIC-5, CIC-6, and CIC-7

7. higher levels of CIC-6 and reduced levels of CIC-7

8. higher levels of CIC-3 and CIC-6 and reduced levels of CIC-7

9. higher levels of CIC-1, CIC-2, CIC-Ka, CIC-Kb, CIC-3, CIC-4, CIC-5, and CIC-6 and reduced levels of CIC-7

10. higher levels of CIC-6 and reduced levels of CIC-3, CIC-4, CIC-5, and CIC-7,

b) methods of screening for compounds, using non-genetically modified in vitro cells.

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
>
> While the art provides guidance for an artisan to arrive at in vitro cells that comprise a transgene construct that overexpresses a gene of interest and at in vitro cells that comprise a transgene construct that reduces expresses of a gene (e.g. a construct used in homologous recombination to disrupt a gene or a construct that expresses antisense), the neither the art nor the specification provides any guidance to arrive at any non-genetically modified cells from any animal, wherein the cell express or do not express specifically named chloride channels. The specification contemplates disruption of an endogenous gene (specification, page 5, lines 19- 30) or the use of antisense (specification, page 6, line 17), and the art teaches that overexpression constructs are commonly used to express a gene of interest. However, there is no guidance for an artisan to use the teachings of the art and specification to arrive at non-genetically modified cells, as encompassed by the claims.
>
> As such, the claims are rejected.".

The Examiner has maintained an objection against all of the claims on the ground of lack of enablement. The Examiner indicates that the claims are enabled for various *in vitro* transgenic cells but objects that they are not enabled for natural cells with high levels of ClC-7 expression compared to other chloride channels or methods of screening using non-genetically modified cells.

In this response, the claims are amended so that they all require genetic modification, which in our submission renders the rejection moot.

> 2. Claims 42-67 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
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> Applicant's arguments filed October 5, 2006 have been fully considered but they are not persuasive.
>
> With regard to use of the phrase, "functionally expressed," Applicant indicates that a channel is functionally expressed if it is a) expressed and b) the form in which it is expressed is such that it is functional (Applicant's response, page 22, 1st parag.). In response, this is not persuasive because as indicated in the Office Action, it is unclear whether

"preferentially functionally expressed" refers to a transgene construct or an endogenous gene that overexpresses CIC-7 (e.g. claim 42) as compared to CIC-3 and/or CIC-6. The phrase is also unclear because it can be interpreted that the cell, while it is preferred that the cell expresses wild type CIC-7 could alternatively comprise a transgene construct that expresses a dominant negative CIC-7. Because it is unclear whether the phrase, "preferentially functionally expressed" refers to a) a transgene construct, b) an endogenous gene, c) wild type CIC-7, or d) dominant negative CIC-7, the claims are ambiguous. It is noted that while the claims, as written, could be interpreted that the cells express dominant negative CIC-7, the specification provides no guidance that this was envisioned in the invention.

Applicant indicates that the phrase, "functionally expressed," is used frequently and is clearly understood in the art. Applicant indicates that US Patent 6,008,437 and 6,562,588 use the term "functionally expressed." In response, in the case of 6,008,437, the patent (e.g. claim 11) uses the term to indicate that the cell has no anthocyanin biosynthesis. There is no ambiguity to whether the claim was referring to a promoter that drove expression of the endogenous gene or to activity of a protein in the biochemical pathway because anthocyanin biosynthesis has to be terminated in order for the claim to be true. Similarly, in the case of 6,562,588, the abstract indicates that the invention is drawn to a CHO cell that does not express sialidase. Again, there is no ambiguity because the abstract indicates that the cell has no sialidase, regardless of whether one may be referring to a gene or a protein.

Applicant indicates that it is clear on the face of the word that if a first name channel is preferentially expressed with respect to a second named channel, there is to be a greater expression of the first than of the second. In response, this is not persuasive because claim 42 could be interpreted either as a) CIC-7 is overexpressed over CIC-3 and/or CIC-6, b) when CIC-3 and/or CIC-6 are expressed in a cell, it is preferred, but not required that CIC-7 is expressed in the cell, or c) it is preferred, but not required, that CIC-7, when it is expressed, it is functional, and that decision is made when CIC-3 and or CIC-6 are present in the cell. While Applicant indicates an intended meaning in Applicant's response, page 22, parag. 4 to page 23, parag. 1, the claims, as written, have multiple meanings that it is unclear what the metes and bound of the claims are.

With regard to the phrase, "reduced functional extent," Applicant indicates that the term is clear on its face. Applicant indicates that if the channel is expressed to a reduced functional extent, one finds that the activity of the channel is reduced either because it is expressed to a reduced extent or because its functionality has been reduced, or both. In response, to clarify the issue, it is unclear what "functional extent" is relative to. For example, in claim 43, the claims can be interpreted as a) the expression levels of CIC-3 and CIC-6 are less than that of CIC-7, b) the expression levels CIC-3 and CIC-6 levels are reduced following an experimental manipulation,

> and c) the expression levels of CIC-3 and CIC-6 are less than that of another population of cells. It is unclear what the intended meaning of the claim is.".

The claims were rejected as lacking clarity on account of the phrase 'preferentially functionally expressed'. The phrase has been removed from the claims in this response, rendering the objection moot. The claims now refer to the expression of functional chloride channels, which is clear.

Moreover, the specification as filed refers extensively to the chloride channels being expressed either functionally or non-functionally as appropriate, see for instance page 1, line 10 for 'not expressed or are expressed non-functionally' and page 4, line 25 for 'expressed functionally'.

The claim language fairly reflects what is actually described.

Objection was also taken to the phrase 'reduced functional extent'. Such an expression is no longer used in the amended claims. The rejection is therefore moot.

The adopted claim language closely reflects the specific subject matter for the Examiner has indicated that the specification is enabling in paragraphs (a) to (k) on pages 3-5 of the official action.

> 3. Claims 42, 43 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Grant and Acosta, 1996, Fundamental and Applied Toxicology, 33: 71-82, as evidenced by Davies et al., 2004, Molecular Vision, 10: 1028-1037.
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> Grant and Acosta teach cultured rabbit corneal epithelial cells (Grant et al., page 73, 1st col., under "Cell culture procedure").
>
> While Grant and Acosta do not specifically teach that CIC-7 is expressed at higher levels than CIC-3 or CIC-6, Davies et al. teach that cultured rabbit corneal epithelial cells express CIC-7 at higher levels than that of CIC-6 (see Davies et al., page 1030, Figure 1A).
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> Thus, Grant and Acosta anticipate claims 42 and 43.
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> Claims 42-44 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Johnson-Muller and Gross, 1987, PNAS, USA, 75: 4417-

4421, as evidenced by Davies et al., 2004, Molecular Vision, 10: 1028-1037.

Johnson-Muller and Gross teach that rabbit corneal stromal cells were cultured (Johnson-Muller and Gross, page 4417 under Materials and Methods).

While Johnson-Muller and Gross do not specifically teach that CIC-7 is expressed at higher levels than CIC-3 and CIC-6, Davies et al. teach that cultured rabbit corneal stromal cells express CIC-7 and that they express less CIC-3 than the epithelial cells and less CIC-6 than that of endothelial cells. Note that the claims only indicate that the cell needs to exhibit a reduction in expression; however, there is no indication as to what the expression is relative.

Thus, Johnson-Muller and Gross anticipate claims 42-43.

Claims 48, 49 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Tamm et al., 1999, Invest. Opthalmol. Vis. Sci. 40: 2577-2582, as evidenced by Comes et al., 2005, Experimental Eye Research, 80: 801-813.

Tamm et al. teach cultured human trabecular meshwork cells (Tamm et al., page 2578).

While Tamm et al. do not specifically teach that CIC-3 is expressed at higher levels than CIC-7, Comes et al. do (Comes et al., page 806, Figure IC).

Thus, Tamm et al. anticipate claims 48 and 49.

Claim 42-46 are newly rejected under 35 U.S.C. 102(b) as being anticipated by anticipated by Gupta et al., 1996, The Journal of Immunology, 157: 2123-2128 as evidenced by Kulka et al., 2002, Inflammation Research, 51: 451-456.

Gupta et al. teach cultured mast cells (Gupta et al, page 2123, under "Mast Cell Source").

While Gupta et al. do not specifically teach that CIC-7 is expressed, but chloride channels CIC-3, CIC-4, CIC-5, and CIC-6 are not expressed, Kulka et al. do (Kulka et at., page 454, Figure B2).

Thus, Gupta et al. anticipate claims 42-46

Claims 42-44, 50-53 are newly reiected under 35 U.S.C. 102(b) as being anticipated by Lee et al., 1998, Am. J. Physiol., 274: L450-L453, as evidenced by Mummery et al., 2005, Can. J. Physiol. Pharmacol., 83: 1123-1128.

Lee et al. teach cultured Calu-3 cells (Lee et al., page L450, 2nd col. under "Methods" to page L451, 1st col., 1st parag.). Mummery et al. teach that Calu-3 cells express CIC-7 more than CIC-3 and CIC-6 and that CIC-4 is

expressed more than CIC-3, CIC-5, CIC-6, and CIC-7 (Mummery et al., page 1126, Figure 2).

Thus, Lee et al., anticipate claims 42-44, 50-53.

Applicants respectfully disagree. Various combinations of claims were rejected as lacking novelty over newly cited documents seemingly selected to show natural cells in which some of the different chloride channels are expressed more than others.

As the claims are now restricted to genetically modified cells, the claimed subject matter in each claim is novel over all of the cited references.

Moreover, none of the art relied upon to show that the natural cells in question had the required pattern of chloride channel expression (Mummery et al; Comes et al; Davies et al; and Kulka et al) was published in time to be prior art in this case.

Applicant submits that all claims are allowable as amended and respectfully request early favorable action by the Examiner. Applicant's representative would like to discuss this case with the Examiner to learn if any outstanding issues remain after consideration of this Amendment. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record. The Applicants believe that a one-month extension of time is required.

The Applicants conditionally petition for a further extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below, charge Deposit Account No. **04-1105** for any required fee.

Dated:

Respectfully submitted,

By _____

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